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ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening conditions with high morbidity and mortality. Supportive care management of SJS/TEN is highly variable. A systematic review of the literature was performed by dermatologists, ophthalmologists, intensivists and gynecologists with expertise in SJS/TEN to generate statements for supportive care guideline development. Members of the Society of Dermatology Hospitalists (SDH) with expertise in SJS/TEN were invited to participate in a modified, online Delphi-consensus. 9-point Likert scale questionnaires regarding 135 statements were administered. The RAND/UCLA appropriateness method was employed to evaluate and select proposed statements for guideline inclusion; statements with median ratings of 6.5-9 and disagreement index ≤1 were included in the guideline. For the final round, the guidelines were appraised by all the participants. An evidence-based discussion and recommendations for hospital setting and care team, wound care, ocular care, oral care, urogenital care, pain management, infection surveillance, fluid and electrolyte management, nutrition and stress ulcer prophylaxis, airway management, and anticoagulation in adult patients with SJS/TEN are included.

CAPSULE SUMMARY

- Supportive care management of SJS/TEN in practice is highly varied.
- The Society of Dermatology Hospitalists presents evidence-based practice guidelines for hospital setting and care team, wound care, ocular care, oral care, urogenital care, pain management, infection surveillance, fluid and electrolyte management, nutrition and stress ulcer prophylaxis, airway management, and anticoagulation for adult patients with SJS/TEN.

BACKGROUND

Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN) spectrum disease (i.e., SJS, SJS-TEN overlap, and TEN) is a rare, severe cutaneous reaction affecting 1.6 to 9.2 patients per million annually in the United States.[1-6] With mortality rates between 15% and 49%,[7-9] early intervention with intensive supportive care is critical, yet the care implemented in practice is highly variable.[10] Standardized SJS/TEN management guidelines are a pressing unmet clinical and research priority.

METHODS

Eleven topics were developed within the scope of the guidelines (**Table 1**). For each topic, PubMed, EMBASE, CINAHL, the Cochrane Library, and clinicaltrials.gov were searched for meta-analyses, clinical trials, open studies, case series, and case reports through November 2018. Articles not written in English were excluded. The search terms and strategies are detailed in **eAppendix1**. The authors identified additional references from manuscript citations, performed detailed evaluation, summarized the literature, and provided level of evidence and strength of recommendations, as indicated in **eAppendix2**. Prior guidelines on SJS/TEN were also evaluated.[11-16]

Experts in SJS/TEN from the Society of Dermatology Hospitalists (SDH) were invited to participate in the modified Delphi process (**eAppendix3**) and to evaluate the level of appropriateness of 135 statements regarding supportive care of patients with SJS/TEN. Using the RAND/UCLA appropriateness method,[17] each statement was evaluated by the 1-to-9 appropriateness rating scale and by the level of disagreement, as measured by a disagreement index (DI). A median appropriateness value of $1 \leq \text{median} < 3.5$ was considered "inappropriate;"

3.5≤ median<6.5 “uncertain;” and 6.5≤median≤ 9.0 “appropriate.” Descriptive statistics were calculated for each item during each round and presented with a histogram (**eAppendix4**). R version 3.6.1 (R Core Team 2019, Vienna, Austria) was used to perform all analyses.

RESULTS

The SDH supportive care practice guidelines for the management of SJS/TEN in adults are presented in **Table 2**.

DISCUSSION

Hospital setting and care team

Specialized care with a multidisciplinary approach is essential to the evaluation and treatment of patients with SJS/TEN.[11,13,14,16] Dermatologists should directly participate in patient management, with input from other specialists with expertise in management of the complications of complex epidermal loss, such as fluid management, wound care, and mechanical ventilation.[18-20] Several small uncontrolled studies have shown decreased mortality with early transfers to burn units or intensive care units (ICU). [21-28] The SDH expert panel recommends care take place in a medical or burn ICU setting, with staff trained in the care of patients with SJS/TEN. A private room with temperature and humidity control and at least 1:1 nursing care is recommended.

Wound care

Wound care for SJS/TEN generally follows current practices in burn management, as strong evidence specific to SJS/TEN is lacking.[29] Percentage body surface area (BSA) of detachable

epidermis is integral to patient prognosis and disease progression.[30] Unlike burn guidelines, which recommend surgical or high-velocity saline debridement of detached epidermis,[12,31,32] the dermatologic SDH expert panel favors a conservative approach to preserve detached epidermis as a biologic dressing, reflecting the different underlying mechanisms involved with SJS/TEN and burn injury.[33] Anti-shear strategies, such as limiting dressing changes, using an air-fluidized bed, and selecting non-adherent dressings, are recommended.[11,16,34] Lysis and careful drainage of large or painful bullae may be performed for comfort only. Gentle cleansing, consisting of sterile water or dilute chlorhexidine with dressing changes, is advised.[35] Application of an emollient such as petrolatum jelly to the skin enhances barrier function, reduces transcutaneous water loss and encourages re-epithelialization.[11,36] Alternatively, modern non-adherent, silver-impregnated primary dressings are recommended for their antibacterial properties, reduced requirement for dressing changes, and improved patient comfort.[29,37-41] Secondary absorptive dressings should be used to control exudate.

Ocular care

Ocular involvement may precede or follow cutaneous disease and occurs in 50-90% of patients.[27,42-48] Acute ocular findings range from conjunctival hyperemia to loss of the entire ocular surface and eyelid margin epithelium.[45,49,50] The severity of ocular involvement disease has not been reliably correlated with the severity of skin disease or SCORTEN.[48,49,51,52]

The SDH expert panel recommends ophthalmic evaluation of all patients with suspected SJS/TEN, even if there is no apparent ocular involvement. Examination should occur during the initial assessment, daily until findings have stabilized, and then the frequency is determined on an individual basis. The entire ocular surface and eyelid margins should be examined with eyelid

eversion, eye rotation and fluorescein staining. Resting eyelid position should be assessed so lagophthalmos can be promptly addressed. Saline may be used to remove loose debris and appropriate tools used to lyse adhesions during daily exams. Grading of ocular findings may aid in medical and surgical decision making (e.g. eAppendix5).[46]

Amniotic membrane transplantation (AMT) has shown to mitigate long-term ocular complications in multiple studies.[51,53-59] AMT should be offered to patients with significant conjunctival, corneal or eyelid margin epithelial defects. If AMT is indicated and not available, a hospital transfer should be considered. Amniotic membrane should cover the entire affected surface including eyelid margins and may need to be replaced over time.

Limited data address the use of topical therapies, including lubricants, anti-inflammatory agents and anti-microbial agents.[15,49,60] For patients without acute ocular involvement, preservative-free artificial tears (AT) should be considered (e.g. AT 4 x/day). Any degree of ocular involvement should prompt high-frequency AT (e.g. AT every 1-2 hours). Topical corticosteroids are used to ameliorate ocular inflammation and may improve visual outcomes.[15,46,59,62] For any degree of ocular inflammation, a topical corticosteroid drop should be applied to the ocular surface (e.g. prednisolone acetate 1%, 2-6 x/day), and a corticosteroid ointment should be applied to the eyelids (e.g. fluorometholone 0.1%, 2-6 x/d). There is limited evidence to guide the use of prophylactic topical antibiotics; however, for patients with ocular epithelial defects, a broad-spectrum topical antibiotic (e.g. Moxifloxacin 0.5%, 3 x/day) should be used. If an ocular infection is suspected, appropriate cultures should be obtained.

Oral care

Oral involvement occurs in 93 to 100 % of patients with SJS/TEN, resulting in pain, impaired oral intake, and poor oral hygiene.[43,63] Long-term complications include sicca syndrome in up to 40% of patients and scarring.[64-66]

All patients with SJS/TEN should have an oral cavity exam on initial presentation and daily thereafter. The use of topical therapies for treating oral involvement in acute SJS/TEN has been adapted from studies in patients with autoimmune blistering diseases involving the oral mucosa, chemotherapy-induced mucositis, and oral graft-versus-host disease (GvHD).[67-71] To provide short-term pain relief and facilitate oral intake, a mouthwash containing a topical anesthetic agent such as lidocaine is recommended.[63] Topical coating agents have been recommended to reduce pain and facilitate healing by covering mucosal ulcerations, such as hydroxypropyl methylcellulose film-forming agents (e.g., Zilactin®), Gelclair®, and Amphojel®.[68]

Oral rinses increase clearance of debris, promote oral hygiene, and improve patient comfort.[68] Antiseptic oral agents are preferred by the SDH expert panel, with a recommendation to consider diluted chlorhexidine.[72] Ultrapotent topical corticosteroids (e.g., clobetasol gel or ointment (0.05%) with or without adhesive bases such as carboximethyl or hydroxyethyl-cellulose, three to four times a day) have been shown to be beneficial in the management of patients with erosive diseases of the oral mucosa[73,69,74-76] and are recommended by the expert panel. Dexamethasone mouth rinse (0.1 mg/mL) or clobetasol propionate 0.05% in aqueous solution, are alternative options. Evidence to support the use of other topical anti-inflammatory agents is lacking.[77]

Urogenital care

Urogenital involvement occurs in approximately 70% of women[78-80] and men[80] with SJS/TEN, resulting in erosions of the scrotum/labia, penis/vulva, dysuria, hematuria, urinary retention, and long-term sequelae such as urethral stenosis and scarring, xerosis, phimosis, dyspareunia, chronic pain, bleeding, sexual dysfunction, infertility, and anxiety.[78-89]

The urogenital tract of all patients with SJS/TEN should be examined upon initial assessment and daily during hospitalization, ideally by a gynecologist, urologist, or urogynecology specialist. The efficacy of treatment strategies has not been adequately studied. Emollients, such as petrolatum, are commonly used to protect inflamed mucosa, reduce adhesion formation, and facilitate healing.[16,80,85] Ultrapotent topical corticosteroids applied to genital lesions during the acute phase may be helpful.[85] If there is clinical suspicion for candidiasis in the setting of vaginal steroid use, consider obtaining a KOH and fungal culture and initiating treatment with antifungal medications.

Insertion of an intravaginal device as early as possible may prevent adhesions and stenosis in those with visible disease.[79] Intravaginal devices should be used regularly until complete healing of lesions and may remain in place for up to 24 hours before being replaced. In patients uncomfortable with using an intravaginal device, medications can be applied twice daily with a vaginal applicator. The role of intravaginal devices in patients without visible disease is uncertain (median 5, DI 0.49).

Menstrual suppression may reduce the risk of vaginal adenosis and endometriosis and can be considered in women with severe genital mucosal involvement.[83,85] Topical estrogen has been shown to promote healing in other vulvar dermatoses and burns and should be considered as adjuvant therapy. [90-94]

Urinary catheters are recommended to decrease pain with urination, prevent urinary obstruction, and monitor fluid balance.[11,80] They should be removed as soon as complete healing occurs and the patient passes a voiding trial. The SDH expert panel recommends topical lidocaine to minimize pain with urinary catheter and vaginal device insertion.

Pain management

Mucocutaneous pain is a key feature of SJS/TEN, occurring in ~ 90% of patients and associated with physical and psychological burden and prolonged hospital stay. It is exacerbated by physical activity, procedures, and dressing changes.[95]

Pain management should be individualized according to pain level and patient comorbidities. Pain level should be evaluated every 4 hours using visual or numeric analog scales.[96]

Wound care strategies that minimize dressing changes are associated with reduced pain.[37,39,97]

Acetaminophen may be sufficient for treatment of mild pain. However, opioid therapy is frequently indicated. Oral synthetic opiates are helpful to control moderate pain. Morphine or fentanyl given enterally, by intravenous bolus, patient-controlled analgesia, or via infusion, may be necessary for more severe pain.[98] Low-dose ketamine infusions may be considered as an alternative or adjuvant therapy for pain in SJS/TEN.[96,99,100] Gabapentin and pregabalin help address neuropathic pain and may decrease opioid consumption in both the acute and healing phases.[101-104] Non-steroidal anti-inflammatory drugs should generally be avoided due to their potential for renal and gastric injury.

Infection surveillance

Infections have been reported in up to 85% of patients with SJS/TEN,[105] and sepsis is the most common cause of death.[106-109] Exposed dermis facilitates bacterial colonization, leading to increased infection risk and impaired re-epithelialization.[11]

The skin should be monitored frequently for signs of infection, such as increasing skin pain.[11] Confusion, hypotension, reduced urinary output, and reduced oxygen saturation may indicate systemic infection.[106,110] In patients in whom infection is suspected, bacterial swabs should be obtained. Slow-healing sites with erosions or vesicles may indicate HSV super-infection, particularly in genital and oral sites; viral swabs should be obtained in such cases.[11] The SDH expert panel did not favor routine performance of skin cultures to guide antimicrobial therapy. Severe ear-nose-throat (ENT) involvement has been associated with pulmonary infection.[111] Evaluation using nasal fiberoptic endoscopy should be considered when dysphonia or dyspnea are present. For intubated patients, there was disagreement and uncertainty (median 5, DI > 1.02) regarding the need of routine fiberoptic bronchoscopy to obtain bronchoalveolar lavage specimens for culture and sensitivity testing, in the absence of signs of infection.[112]

Hand hygiene and hospital infection control measures should be followed to prevent infection. Prophylactic antibiotic coverage in the absence of proven or suspected infection may select for resistant organisms and contribute to increased mortality.[113] Antibiotic-therapy should be tailored to culture data[12,113,114] and local antibiogram.[115] Data suggest *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* organisms are the most common causes of blood stream infection in SJS/TEN.[106]

Patients with SJS/TEN may develop neutropenia, especially in severe cases.[116,117] The role of recombinant human G-CSF in this setting is uncertain (median 5, DI 0.32).[118,119]

Fluid management and electrolytes

Electrolytes abnormalities occur in approximately 20% of patients with SJS/TEN.[95] Due to extensive skin failure, patients may have large insensible losses.[11] Oropharyngeal lesions contribute to decreased oral intake. Electrolytes can be lost in blister fluid, which is rich in sodium, potassium, and chloride.[13] Hypophosphatemia is also common.[13] Fluid balance and electrolytes should be monitored daily to ensure adequate correction during treatment.[120]

Fluid resuscitation in SJS/TEN is adapted from the management of burn patients, though fluid losses, in general, are less.[121] Current evidence supports the use of crystalloid for resuscitation, though there are no prospective data to guide fluid selection.[121-123] Evidence regarding colloid fluids and albumin is controversial,[121,124-127] and their use was considered uncertain by the expert panel (median 6, DI 0.65). Appropriate calculation of fluid resuscitation volume based on the percent of detached skin was also uncertain (median 5, DI 0.55) .[14,123,126] The expert panel recommended resuscitation be guided by physiologic parameters, with a target urine output of 0.5 – 1 mL/kg/hr.[25,128,129]

Nutrition and stress ulcer prophylaxis

Caloric requirements in SJS/TEN are increased.[11] Caloric intake should be 30-35 kcal/kg.[13] In patients unable to eat, a nasogastric tube should be used to provide enteral nutrition unless there is involvement of the nasopharyngeal mucosa.[130-132]Enteral nutrition is preferable to prevent stress ulcer formation and infectious complications.[133] If adequate nutritional requirements cannot be met enterally, parenteral nutrition can be used to supplement deficiencies,[99,134] however it has been associated with higher mortality rates.[135]

Hyperglycemia is common in SJS/TEN and is associated with increased mortality, therefore, careful glucose monitoring to ensure adequate glycemic control is recommended.[131] Tight glycemic control regimens (serum glucose 80–110 mg/dl) have been associated with increased hypoglycemic events and mortality among adults in the ICU; thus, glycemic control regimens maintaining glucose levels between 110 -180 mg/dl are preferable.[136-139]

In patients receiving enteral nutrition, pharmacologic stress ulcer prophylaxis (SUP) is not recommended based on studies performed in ICU patients.[140-142]

Airway management

Patients with SJS/TEN may experience sloughing of the respiratory tract epithelium which cannot be predicted by the extent of cutaneous involvement.[11] Chest x-ray and arterial blood gas measurement should be obtained as part of the baseline evaluation.[16,143-145] Appropriate pulmonary toilet and positioning may help keep the upper airway clear.[13] Attention should be paid to the nose to maintain a clear respiratory passage.

Patients with hypoxemia, dyspnea, or tachypnea should undergo fiberoptic bronchoscopy to evaluate the extent of bronchial involvement while minimizing iatrogenic trauma.[145,146]

Pulmonary function testing and computed tomography scanning are indicated in those with ongoing respiratory symptoms.[14,147]

Patients with SJS/TEN may experience airway compromise requiring intubation and early tracheostomy (before ventilator day 10) prior to the onset of respiratory failure, predicted by oral mucosal involvement and initial BSA of 70% or more, progression of BSA from hospital day 1 to hospital day 3 by 15% or more, neurologic diagnosis preventing airway protection, or documented airway involvement on direct laryngoscopy.[148] Improved survival is attributed to

aggressive wound care after airway protection. Ventilation strategies should mimic those used in acute respiratory distress syndrome, such as low tidal volume[149] and early prone positioning.[144,150]

Anticoagulation

Patients with SJS/TEN are at increased risk of venous thromboembolism. Prophylaxis with low weight molecular heparin is recommended.[151-154] Patients who are bleeding or at high risk of major bleeding should receive graduated compression stockings or intermittent pneumatic compression instead.[152,154] Early mobilization of patients should be encouraged.[155]

LIMITATIONS AND CONCLUSION

These guidelines address supportive care treatment options for adult patients with SJS/TEN. Systemic treatment options, management of sequelae, and considerations in special populations (e.g., pediatric, pregnant) will be addressed in future guidelines. Judgment regarding the appropriateness of any specific therapy lies with the treating clinician. Future studies will necessitate revisions and updates to these recommendations.

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Table 1. Clinical Question

What supportive care treatment strategies are safe and effective for adult patients with SJS, SJS-TEN overlap, or TEN?

1.	Hospital setting and care team
2.	Wound care
3.	Ocular care
4.	Oral care
5.	Urogenital care
6.	Pain management
7.	Infection surveillance
8.	Fluid and electrolyte management
9.	Nutrition and stress ulcer prophylaxis
10.	Airway management
11.	Anticoagulation

SJS, Steven-Johnson syndrome; TEN, toxic epidermal necrolysis

Table 2. Recommendations

	Level of evidence*	Strength of Recommendation*	DI**	Median
Hospital setting and care team				
Management of patients with SJS/TEN requires a multidisciplinary team that may include dermatology, intensive care, pulmonology, ophthalmology, otorhinolaryngology, gynecology, urology, nephrology, plastic surgery, nutrition, nursing, psychology/psychiatry, and other fields.	4	D (GPP)	0.00	9.0
Dermatologists are experts in the disease state of SJS/TEN and should directly participate in the management of such patients.	4	D (GPP)	0.00	9.0
Staff should have specific training in the care of patients with SJS/TEN.	4	D (GPP)	0.13	9.0
Chronic conditions and comorbidities play a significant role in the mortality of SJS/TEN patients and the need for specialized care, and hospital transfers should take into account these comorbidities.	3	C	0.00	9.0
Medical or burn ICU settings of care for SJS/TEN patients are recommended.	2-/3	D	0.00	9.0
SJS/TEN patients must be cared for in a private room.	3	D	0.13	9.0
Patient rooms should be controlled for humidity.	4	D	0.26	7.5
Sterile sheets should be obtained and used for patient bedding, where available	4	D	0.65	8.0
At least one nurse should take care of one SJS/TEN patient (at least 1:1 ratio).	4	D	0.32	8.0
Wound care				
Determine % BSA of epidermal detachment (only skin that is already necrotic, detached, or skin with positive Nikolsky sign).	3	D	0.06	9.0
Avoid unnecessary wound manipulation by limiting the number of dressing changes.	3	D	0.13	8.0
Use an air-fluidized bed to minimize friction.	3	D	0.15	8.0
Gently cleanse all areas with sterile water, normal saline, or dilute chlorhexidine (0.05%) solution with dressing changes.	4	D	0.26	8.0
The detached and detachable epidermis should be left in place as a biological dressing.	4	D (GPP)	0.13	8.0
Lyse large or painful bullae for comfort only.	4	D (GPP)	0.20	8.0
Wound debridement of necrotic skin is not recommended.	4	D (GPP)	0.82	7.0
Apply topical emollients such as petroleum jelly on the entire epidermis.	3	D	0.13	8.5
Apply non-adherent sterile dressings to denuded skin.	3	D	0.13	9.0
Select non-adherent silver-impregnated primary dressings for optimal moisture retention and antibacterial properties.	2+/3	D	0.59	6.5
Apply secondary dressing to absorb exudate.	3	D	0.37	7.0
Ocular care				
Patients thought to have SJS/TEN should be examined by an ophthalmologist as part of the initial assessment.	4	D (GPP)	0.00	9.0
Patients should be examined at least every 24 hours until it is clear there is no worsening, and thereafter the frequency of follow-up should be determined on a case-by case basis.	4	D (GPP)	0.13	9.0
Educate the appropriate staff regarding the need for immediate ophthalmologic evaluation of all SJS/TEN	4	D (GPP)	0.00	9.0

patients and the proper application of topical ocular medications (drops and ointments).				
The entire ocular surface should be examined daily- eyelid skin, eyelid margin, conjunctiva, and cornea. The eyelids should be everted, and the eyes rotated to look for forniceal and tarsal conjunctival epithelial defects and early symblephara.	4	D (GPP)	0.13	8.0
Fluorescein staining should be done in all patients.	4	D	0.65	6.5
Resting eyelid position should be assessed for lagophthalmos.	4	D	0.37	8.0
Grade the ocular exam findings to facilitate medical decision making (eAppendix5).	3	D	0.65	7.0
Consider amniotic membrane transplantation (AMT) during the initial evaluation of any patient thought to have SJS/TEN and at each follow-up exam during the acute phase.	1+/2+	B	0.13	8.0
Offer AMT to patients with moderate to severe conjunctival injection, significant conjunctival epithelial defects (especially the eyelid margin, tarsal conjunctiva, fornices), significant corneal epithelial defects or membranes / pseudo-membranes.	1+/2+	B	0.13	8.0
AMT is ideally performed within 5 days of onset but may be offered later.	1+/2+	B	0.13	8.0
Amniotic membrane should cover the entire ocular surface.	1+/2+	B	0.00	8.0
Apply artificial tears every 1-2 hours for any patient with any ocular surface inflammation.	4	D	0.13	8.0
Apply ophthalmic ointment to the eyelid margin every 2-24 hours.	4	D	0.13	8.0
Eye drops containing preservatives should be avoided.	4	D	0.48	8.0
Apply a moisture chamber over the eyes for lagophthalmos. A facemask or moist occlusive dressing may be used for this purpose.	4	D	0.56	8.0
Rinse the eyes every 2-24 hours with sterile saline.	4	D	0.16	7.5
Remove/lyse adherent debris and membranes daily.	4	D	0.16	8.0
Apply a topical anesthetic (e.g. proparacaine or tetracaine) if needed.	4	D	0.12	8.0
Apply a corticosteroid containing ointment to the eyelid margin and eyelashes at least once daily and a corticosteroid drop to the ocular surface at least twice daily for any patient with any ocular surface inflammation.	2-	D	0.59	8.0
If there is clinical suspicion of infectious conjunctivitis, obtain a bacterial (and consider a fungal) culture of the ocular surface and begin application of a topical broad-spectrum antibiotic (4th generation quinolone commonly used).	4	D	0.00	8.0
Avoid chloramphenicol drops and tetracycline containing ointment, as these have been associated with late complications, particularly dry eyes.	3	D	0.65	8.0
Oral Care				
The mouth should be examined as part of the initial assessment of a patient with SJS/TEN.	4	D (GPP)	0.00	9.0
Daily oral exam is required during acute illness.	4	D (GPP)	0.00	9.0
Have a low threshold for HSV PCR, bacterial, and fungal cultures if infection is suspected.	4	D (GPP)	0.00	9.0
Petrolatum ointment should be applied on the lips immediately, and then every 2 hours throughout the acute illness.	3	D	0.29	8.0
Viscous lidocaine 2%, 15 ml per application, can be used every three hours (and prior to cleanses) as an oral rinse to control pain.	3	D	0.13	8.0
Clean the mouth daily with warm saline mouthwashes or an oral sponge, sweeping the sponge gently in the labial and buccal sulci to reduce the risk of fibrotic scars and prevent buildup of hemorrhagic crust.	3	D	0.13	8.0

An antiseptic oral rinse should be used twice daily to reduce bacterial colonization of the mucosa.	3	D	0.65	6.5
A topical steroid (ultrapotent) ointment can be applied up to 4 times a day during the acute phase.	3	D	0.58	8.0
Consider diluted chlorhexidine digluconate mouthwash (2-3 times daily).	3	D	0.37	7.0
Consider the use of oral coating agents for pain reduction in patients with oral mucosal involvement.	4	D	0.13	8.0
Urogenital care				
Examine the urogenital tract as part of the initial assessment of a patient with SJS/TEN.	4	D (GPP)	0.00	9.0
Urogenital exam should ideally be performed by a gynecologist, urologist, or urogynecology specialist.	4	D (GPP)	0.13	8.0
Daily exam is required during the acute illness.	4	D (GPP)	0.13	8.0
If there is clinical suspicion for vaginal candidiasis in the setting of vaginal steroid use, consider obtaining a KOH and fungal culture and beginning treatment with antifungal medications.	4	D (GPP)	0.13	8.0
During the acute phase of the disease, the vulvar/urogenital skin/mucosa should be coated with an ointment and/or ointment gauze to help reduce pain, reduce adhesion formation, and facilitate healing.	3	D	0.13	8.0
An intravaginal device such as a dilator/tampon/vaginal mold/roll of gauze covered in a lubricated condom can be utilized to treat vaginal disease.	3	D	0.13	9.0
Intravaginal devices may be left in place for no longer than 24hrs, at which time they should be replaced.	3	D	0.03	8.0
Even for virginal patients, use of a small mold or a condom-covered tampon should be encouraged if the patient is emotionally and physically comfortable with the regimen.	4	D	0.65	7.0
Patients uncomfortable with using an intravaginal device, can apply medication twice daily with a vaginal applicator.	4	D	0.06	8.0
Topical anesthetics (i.e., lidocaine 5% ointment) can be used at the vaginal introitus, once open sores have healed, to reduce discomfort with use of the vaginal dilators.	3	D	0.01	8.0
It is at the provider's discretion to use either a non-steroidal ointment (i.e., petrolatum jelly) with reapplication as frequently as necessary (2-4x daily) to maintain barrier protection and/or consider 1-2x daily application of a high potency steroid ointment if active inflammation is observed, with the caveat that consideration for tapering of steroid use should be based on clinical improvement.	3	D	0.00	8.0
Consider the medication on the dilator can be changed to, or alternated with, estrogen cream to help promote healing of the vaginal mucosa.	4	D	0.55	7.0
Consider menstrual suppression to reduce discomfort and possibly to decrease the risk of vaginal adenosis.	3	D	0.69	8.0
Consider division of any fine [vaginal] adhesions to prevent the development of thick fibrous bands that could lead to problems inserting tampons and during sexual intercourse later in life.	3	D	0.22	8.0
Consider urinary catheters to decrease pain with urination, prevent urinary obstruction, and monitor fluid balance.	3	D	0.13	8.0
Pain management				
Evaluation and treatment of pain is a priority in the acute phase, especially during wound management.	4	D (GPP)	0.00	9.0
Pain should be evaluated on a 4-hourly basis.	4	D (GPP)	0.13	9.0
A validated pain tool should be used to assess pain in all conscious patients at least once a day.	4	D (GPP)	0.13	9.0
If the score is mild, pain control with acetaminophen should be introduced.	3	D	0.00	8.0
If acetaminophen is not enough, oral synthetic opiates such as tramadol should be considered.	3	D	0.23	8.0
If the pain score is moderate to severe, then morphine or fentanyl should be delivered enterally, by PCA, or by infusion.	3	D	0.13	8.0

Procedures such as dressing changes and bathing may require additional pain control.	3	D	0.00	9.0
Consider adding low dose ketamine infusions.	3	D	0.65	6.5
Consider adding gabapentin or pregabalin.	3	D	0.65	7.0
NSAIDs should be avoided due to renal or gastric injury.	3	D	0.35	7.0
Infection surveillance				
Hand hygiene and other infection control measures should be strictly applied.	3	D (GPP)	0.00	9
Patients should be monitored carefully for signs of systemic infection, such as confusion, hypotension, reduced urine output and reduced oxygen saturation.	3	D	0.00	9
Cutaneous infection may be accompanied by increase in skin pain.	3	D	0.13	8.5
Consider activation of HSV in eroded or vesicular areas which are slow to heal, particularly in genital and oral sites. Take viral swabs if herpes virus infection is suspected.	3	D	0.00	9
In patients with diarrhea who are immobile, consider a fecal management system to prevent fecal soiling of wounds.	3	D	0.13	8.5
Prophylactic antibiotic treatment is not recommended.	4	D	0.13	8.5
Administer systemic antibiotics only if there are clinical signs of infection. The choice of systemic antibiotic should be guided by local microbiological resistance patterns.	3	D	0.13	9
Severe ENT involvement is significantly associated with pulmonary infection. ENT evaluation using nasal fiberoptic endoscopy should be suggested when dysphonia or dyspnea are present.	3	D	0.16	8.0
Fluid and electrolyte management				
Peripheral catheters preferred for vascular access with implantation in uninjured skin and fixed with non-adhesive dressings.	3	D	0.13	9
Change peripheral venous cannulas every 48 hours if possible.	3	D	0.65	7
Monitor electrolytes and fluid balance daily.	4	D (GPP)	0.00	9
Consider invasive fluid balance monitoring with Foley catheter.	3	D	0.33	8
Fluid administration should be titrated to urine output (0.5-1 ml/kg/hr).	3	D	0.16	8
Nutrition and stress ulcer prophylaxis				
Maintain adequate nutrition orally; utilize nasogastric tube if necessary. Enteral feeding reduces stress ulcers and reduces bacterial translocation and enterogenic infection.	3	D	0.13	9
Supplement enteral nutrition with parenteral if intake via the enteral route is insufficient to meet caloric needs.	3	D	0.39	8
Avoid nasogastric tube placement if there is involvement of the nasopharyngeal mucosa.	3	D	0.37	7
Deliver daily caloric requirement of 30-35 kcal/kg.	3	D	0.33	8
Maintain close glycemic control.	3	D (GPP)	0.03	8
In patients receiving enteral nutrition, pharmacologic stress ulcer prophylaxis is not recommended.	4	D (GPP)	0.65	8
Pharmacologic stress ulcer prophylaxis with PPIs should be limited to patients at high risk for clinically important bleeding (respiratory failure, coagulopathy, liver disease, use of renal replacement therapy, three or more co-existing diseases).	4	D (GPP)	0.16	8
PPIs should be used over H2 receptor antagonists (due to decrease in GI bleeding events).	4	D (GPP)	0.5	7.5
Airway management				
The nose should be examined as part of the initial assessment of a patient with SJS/TEN.	4	D (GPP)	0.13	9

Daily nasal exams are required during acute illness.	4	D (GPP)	0.07	8
Pulmonary care includes normal saline aerosols, bronchial aspiration and postural drainage by turning the patient to different sides.	4	D	0.11	8
Severe ENT involvement is significantly associated with pulmonary infection. ENT evaluation using nasal fiberoptic endoscopy should be suggested when dysphonia or dyspnea are present.	3/4	D	0.16	8
Chest X-ray and arterial blood gases should be obtained upon admission for baseline respiratory function assessment.	3/4	D	0.65	7
Patients with ongoing respiratory symptoms should be closely monitored with pulmonary function testing and high-resolution computed tomography (CT) scanning.	3	D	0.37	8
Fiberoptic bronchoscopy should be undertaken in patients with respiratory symptoms and hypoxia.	3	D	0.00	8
Bronchoscopy should be done by an experienced technician due to risk of post-instrumental endobronchial bleeding.	3	D	0.13	8
Consider intubation and early tracheostomy in patients with oral involvement AND one of the following: • Initial BSA 70% or more • Progression of BSA involved from DOH1 to DOH3 > 15% • Underlying neurologic diagnosis prevents airway protection • Documented airway involvement on direct laryngoscopy	3	D	0.40	7
Ventilation strategies should mimic ARDS management guidelines (low tidal volume and early prone positioning).	4	D	0.65	7
Anticoagulation				
Immobile patients should receive low molecular weight heparin.	4	D (GPP)	0.07	8
For acutely ill patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression is recommended.	4	D (GPP)	0.16	8

*For level of evidence and grade of recommendation calculation see eAppendix2. GPP, good practice point. A GPP is a recommendation for best practice based on the experience of the guideline development group.

**Statements were appraised on a Likert scale of 1 (strongly disagree) to 9 (strongly agree), medians and disagreement indexes (DI) were calculated for each statement. Items with a DI≤1 and a median≥6.5 were deemed appropriate and included in the guidelines, and all other items were not included as recommendations. (eAppendix4)

SJS, Steven-Johnson syndrome; TEN, toxic epidermal necrolysis; BSA, Body Surface Area; DI, disagreement index; DOH, Day of hospitalization; ENT, Ear-Nose-Throat; ICU, Intensive Care Unit; NSAIDs, Non-steroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; PPI, proton pump inhibitor.